neurofibromatosis, Huntington's disease, depression, amyotrophic lateral sclerosis, multiple sclerosis, stroke, Parkinson's disease and multiple infarcts dementia.

15. (Amended) A method for identifying patients diagnosed with a neurological disease for participation in clinical trial of a drug for the treatment of said neurological disease, said method compromising:

a) identifying a patient already diagnosed with said neurological disease;

b) determining the *apoE* allele load of said patient by genotyping or phenotyping, said phenotyping including characterizing ApoE protein isoform; and

c) converting the data obtained from step b) into a prognostic protocol, wherein a patient lacking at least one *apoE4* allele or at least one ApoE4 protein isoform is a desired candidate for a drug trial for said neurological disease.

REMARKS

Summary of the Invention

The present invention features a method for determining the appropriate therapy and/or prognostic protocol for a patient with a neurological disease. The invention also provides a method for identifying human patients with a non-AD neurological disease who are likely to respond in clinical trials that test pharmaceuticals useful in the treatment of such a disease. This determination or identification is performed by determining the patient's *apoE* allele load, where the presence of an *apoE4* allele or ApoE4 protein isoform is indicative of a poor patient outcome or decreased efficacy of a therapeutic.

Summary of the Office Action

Claims 1-16 are pending. Claims 1-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 1-14 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The rejections are addressed below.

Support for the amendments

This application is a continuation from U.S. application serial no. 08/766,975, filed December 16, 1996, which is a continuation-in-part, claiming priority from U.S. application serial no. 08/727,637, and was co-pending to the national phase application of international application no. PCT/CA95/00240, filed April 26,1995.

Support for the amendments to independent claims 1 and 15 can be found throughout the specification. Specifically, *apoE* genotyping can be found on page 13, lines 11-25, and phenotyping of ApoE protein can be found on page 14, lines 5-16. Support for the analysis of *apoE4* allele or ApoE protein isoform in step c) of amended claims 1 and 15 can be found in Example III on pages 18-21.

Amendments to dependent claims 3, 8, and 9 were made to now correctly depend on claim 1 or to correct a deficiency in the antecedent basis (claim 6). No new matter is added.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

The Examiner has rejected claims 1-16, as being indefinite for failing to clearly provide all the salient features of the claimed methodology. Specifically, the Examiner states that the claims fail to set forth a correlation between *apoE* allele load and drug efficacy prediction, *apoE* allele load and drug responsiveness, and/or prediction to therapeutic treatment based on *apoE* allele load.

Applicant has canceled claims 2 and 16 and amended independent claims 1 and 15 to further include in step b), the determination of the presence or absence of the *apoE4* allele or ApoE4 protein isoform in a patient already diagnosed with a neurological disease. Further, the claims have been amended to also recite that the presence of at least one *apoE4* allele or ApoE4 protein isoform is correlated with poor patient outcome or

decreased responsiveness to therapy, and is the basis for identifying candidates for participation in clinical trials.

The claims as presently written, clearly provide the salient features comprising a prognostic protocol. Accordingly, this rejection may now be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-14 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states that the present application fails to provide adequate guidance and support to establish a relationship between *apoE* allele load and the various neuropathologies claimed.

The Examiner further cites Timchenko *et al.*, 1996, Salvatore *et al.*, 1995, and Brouillet *et al.*, 1995 as examples in which the prior art teaches that the underlying mechanisms for many of these disorders remain obscure. Thus, the Examiner posits that it is not apparent how measurement of *apoE* allele load would be predictive of an effective therapy. Finally, the Examiner asserts that the present application fails to provide any working embodiments, which, when taken in view of the unpredictability of the prior art, would require undue experimentation. Applicant respectfully traverses this rejection.

Applicant has established that neurons possessing the *apoE4* allele are less likely to recover and/or respond well to chemotherapeutics (Example III, pages 18-21, of the specification). The allowability of the pending claims is not contingent on establishing a direct relationship between *apoE* allele load and various specific neuropathologies since Applicant has shown by his discovery that any neuronal insult or pathology is likely to be exacerbated in an ApoE4 patient. The *apoE* genotype of a patient determines, independent of disease, the ability of their neurons to respond to a chemotherapeutic (e.g., a cholinomimetic). Applicant teaches that the measurement of the *apoE* allele load correlates with the ability of a patient to respond to a representative drug (for instance, tacrine). Therefore, Applicant has met the Examiner's test that correlates *apoE* measurement with the ability of a patient to respond to treatment with a therapeutic.

As to the Examiner's assertion that the prior art teaches that the underlying disease mechanism(s) of many neurological disorders have yet to be elucidated, Applicant does not deny that some of the disease mechanisms of these disorders are not fully understood. However, Applicant's claimed invention is not directed at elucidating or necessarily preventing the peculiar causative mechanism of any one disease. Rather, the claimed invention is directed at predicting the likely responsiveness of patients with a particular *apoE* genetic background to treatment for a diagnosed neurological disease. More specifically, the claimed invention is directed at determining the *apoE* allele load of a patient diagnosed with a neurological disease and using the observation of the presence of an *apoE4* allele or ApoE4 protein isoform as an indication that the patient may have a poor outcome such as low apparent responsiveness to a therapeutic (for example, a cholinomimetic). In other words, the invention is focused on the prediction of the general responsiveness of neurons in an individual based upon genotype and how this responsiveness can be exploited to predict outcome of a patient with a neuropathology.

Finally, the Examiner asserts that the disclosure lacks any working embodiments directed to neuropathologies. Applicant disagrees and directs the Examiner's attention to Examples II, III, and V of the specification. Example II (starting on pages 17 and including Fig. 3), demonstrates the correlation between *apoE4* allele load with senile plaques and neurofibrillary tangles. Example III (starting on page 18 and including Figs. 4 and 6), demonstrates the association between neurolopathologies, choline acetyltransferase activity (ChAT), and *apoE* allele load. This study, conducted on post-mortem AD subjects, demonstrated that significant reduction in ChAT activity is observed in *apoE4* carrier patients. Furthermore, this study also demonstrated the impact of allele dosage of *apoE* on ChAT activity. ChAT activity was assessed in AD and non-AD subjects and was shown to follow a gradient according to the *apoE* genotype, i.e., non-AD *apoE3/apoE3* > AD *apoE3/apoE3* > AD *apoE3/apoE4* > AD *apoE4/apoE4*.

In Example V (starting on page 28 and including Fig. 8), a thirty-week study was undertaken to evaluate *apoE* allele load on AD diagnosed patients receiving treatment with the acetylcholinesterase inhibitor, tacrine. Using clinically accepted criteria to

assess drug responsiveness, the impact of the different *apoE* genotypes (*apoE2/apoE2*, *apoE2/apoE3*, *apoE3/apoE3*, *apoE3/apoE4*, and *apoE4/apoE4*) was evaluated. The results clearly showed that four out of five patients that were unresponsive to tacrine therapy carry at least one copy of the *apoE4* allele.

The above examples clearly provide sufficient examples to establish that the *apoE* genotype (or ApoE protein isoform phenotype) is a useful criteria to develop a prognostic protocol for appropriate therapy in neurological diseases. Such a working embodiment is in compliance with the criteria conveyed in the M.P.E.P. § 2164.02, which states,

> "Compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic." A working example is based on work actually performed. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved."

As the present invention is directed at predicting the likely therapeutic responsiveness of patients with a particular *apoE* genetic background, and independent of neurological disease, Applicant has demonstrated adequate guidance and support for one skilled in the art to practice the claimed invention. Accordingly, this rejection may be withdrawn.

CONCLUSION

Applicants submit that this case is in condition for allowance, and such action is respectfully requested. If the Office does not concur, a telephonic interview with the undersigned is hereby requested.

A marked-up version indicating the amendments to the claims, as required by 37 C.F.R. § 1.121 (c)(1)(ii), is enclosed.

A clean version of all pending claims is also enclosed.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: September 13, 2002

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